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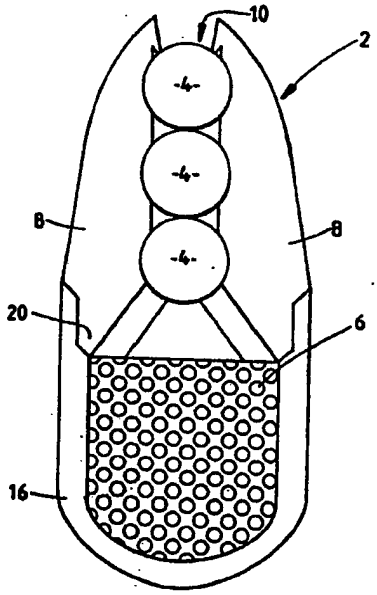
(54) Title: INTRA-RUMINAL DEVICES

(57) Abstract

A device for the administration of substance into the rumen of an animal comprises a body (2) having an open structure within which is retained at least one pellet (4) of the substance. The pellet (4) has an outer impervious coating which degrades when exposed to the action of ruminal fluid to permit subsequent release of the substance. Preferably, the device contains a group of such pellets (4) with the degradation times of the layers of the respective pellets being different whereby to permit release of substance from the group of pellets (4) in a timed sequence.



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INTRA-RUMINAL DEVICES

The present invention relates to an intra-ruminal device for the delivery of a substance into the rumino-reticular sac of a ruminant animal.

It is well known to administer nutrients and/or therapeutic materials to ruminant animals such as cattle and sheep by oral administration of the substance bolus into the rumino-reticular sac of the animal. Substances administered in this way include vitamins, food and mineral substances, anti-parasitic agents, parasiticides, larvicides, biocides, anti-infection agents, flukicides, and growth promotants. The substance may be introduced into the rumen by a device which carries the substance and which provides sustained release of the substance within the rumen. After delivery of the substance has been completed, the residue of the device is expelled. Conventional devices of this type usually provide continuous release of the substance over a substantial period of time commencing shortly after administration. However, a more efficient and effective treatment may be obtained if the substance is released in a more controlled pulsatile or periodic manner.

According to the present invention there is provided a device for release of substance into the rumen of an animal, said device comprising a body carrying at least one pellet including substance to which access of ruminal fluids is initially prevented by an impermeable barrier which degrades when exposed to ruminal fluids, the body having an open structure to permit contact of ruminal fluids with the or each of the pellets, and said device being such that the device will remain within the rumen for a period of time sufficient to enable release of substance from the or each of the pellets.

The device may be retained within the rumen for the required time by means of the density of the device. Alternatively, or in addition, retention of the device can be effected by means of the geometry or physical features of the device which may be such, when in the rumen, as to resist expulsion and for this

purpose the device may have a geometry which changes, when in the rumen, to resist expulsion. By way of example this effect could be achieved by means of expandable wings on the device, and/or the device may carry external hairs, filaments, or other means which act to resist expulsion from the rumen for a period of time sufficient to ensure release of the substance.

The substance may be released in a single pulse or dose and for this function only a single pellet will be required. The characteristics of the impermeable barrier can be varied to determine the time at which release occurs after administration.

When it is required to release the substance in a plurality of spaced pulses, which may be desirable for the treatment of certain conditions, the device can contain a single pellet consisting of alternating impermeable layers and layers of substance. Alternatively, and as is preferred for simplicity of manufacture, the device can contain a plurality of pellets mounted within the body such that the ruminal fluids can contact each of the pellets simultaneously, the impermeable barrier of the respective pellets being such that the time required to degrade the barrier differs from pellet to pellet.

The impermeable barrier of the or each pellet is preferably provided by an outer coating of a suitable polymeric material. When the device contains a plurality of pellets as described above, to provide release in a plurality of spaced pulses, the thickness and/or composition of the coating of the different pellets of the group will vary whereby to provide different degradation rates. The open structure of the body may be a cage-like structure in which the pellets are located in discrete positions such that at least a part of the outer surface of each pellet is capable of contact by ruminal fluids.

When retention of the device within the rumen is provided wholly or partly by the density of the device, the required density of the device is preferably provided by ballast which is released after the required period of time to permit

expulsion of remaining parts of the device. Advantageously this is achieved by enclosing the ballast within a housing which forms part of the body. The ballast includes material which is broken down on contact by ruminal fluids. The device includes means for preventing contact of ruminal fluids with the ballast until such time that expulsion is required. In one preferred form, this effect may be achieved by positioning one pellet to block a fluid access passage to the ballast until substantial dissolution of the pellet has occurred. Alternatively, the ballast housing, part of the housing, or a closure for the housing may be formed from a material which degrades over a period of time to then permit contact of ruminal fluids with the ballast.

The components forming the body of the device are preferably constructed from polymeric material which will degrade, for example exposure to ultra-violet radiation or bacterial action, after expulsion.

An embodiment of the invention will now be described, by way of example only, with reference to the accompanying drawings in which:-

Figure 1 is a side view of a preferred embodiment of an intra-ruminal device in accordance with the invention;

Figure 2 is a longitudinal section of the device;

Figure 3 is an exploded longitudinal section of the device;

Figure 4 is a plan view of the device;

Figure 5 is an underneath view of a cage-like structure which forms part of the body of the device; and

Figure 6 shows a graph of absorption of the dyes Pontamine Sky Blue (-♦ -) and Orange G (-◊ -) from pellets coated with different biodegradable polymers plotted against time of incubation in a medium containing 0.1 M NaOH, 10% Ethanol and 0.9% NaCl.

As shown in the accompanying drawings a device for providing pulsed release of substance in a plurality of spaced pulses into the rumino-reticular sac

comprises a carrier 2 for a plurality of discrete pellets 4 which are constructed in a manner to be described so that the substance is released from the different pellets in a spaced sequence so as to provide the required pulsed delivery. The device also contains ballast 6 which retains the device in the rumino-reticular sac until such a time that the final pulsed release of substance has taken place whereon the density of the device decreases to such an extent as to permit easy expulsion by regurgitation or passage through the alimentary tract.

The carrier 2 comprises an open cage-like structure containing the required number of pellets 4. In the device shown there are three pellets 4 although there may be more than three or fewer than three, according to requirements. In the particular form shown, the cage-like structure is defined by an annular array of radial fins 8, the inner edges of which define a central longitudinal passage 10 in which the pellets 4 are located in longitudinally-spaced relation. The inner edges of the fins 8 are shaped to define seats 12 in which the pellets 4 can be positively located, for example by a snap action. With this construction, substantially the entire surface area of each pellet 4 is exposed to contact by ruminal fluids which are able to flow freely between the fins 8 and into simultaneous contact with the pellets 4 within the central passage 10. Although this form of cage is preferred, it is to be understood that other forms of cage and other forms of open structure which permit contact of each of the pellets simultaneously with the ruminal fluids can be provided.

The required pulsed release is obtained by providing each pellet 4 with a degradable, impermeable, outer barrier which degrades when contacted by ruminal fluids over a predetermined period of time to then provide access of the fluids to the active or other substance which provides the main body or core of the pellet. By varying the thickness and/or the nature of the outer degradable barrier, the time required within the rumen to degrade the barrier will vary. Accordingly, a pulsed release can be obtained by using a group of pellets in which the barrier on each pellet is different so that the barrier on one of the pellets is able to break down relatively quickly to then permit release of the substance from

that pellet, with the barriers of the remaining pellets breaking down at a much slower rate. At a predetermined time within the rumen, the barrier of another one of the pellets will break down sufficiently to permit release of substance from that pellet and the characteristics of the barrier of that second pellet are determined such that release of the substance does not occur until a predetermined period of time after release of substance from the first pellet has been completed. Likewise, the characteristics of the barrier of the third pellet are such that release of substance from that pellet will not occur until a predetermined period of time after release of substance from the second pellet has been completed; similar considerations apply to any further pellets which might be carried by the device. Accordingly, by appropriately selecting the degradation characteristics of the barrier of each pellet a required release sequence can be obtained at spaced intervals in time. As a non-limiting example of the release sequence, the first pellet can be designed to release substance over a period of a few hours or a few days at 4 weeks after administration, the second pellet acting similarly at 8 weeks and the third pellet acting similarly at 16 weeks after administration.

Each pellet is manufactured by forming a core containing the active or other substance. The core may be spherical (as shown) but may alternatively be of another shape. The core is produced by standard manufacturing techniques similar to those used in the manufacture of items of confectionery. The core is then coated to build up the mechanical strength of the pellet with, for example a mixture of starch, sugar, and water and is air-dried. The coating can be applied by a pan-coating process which produces pellets of regular spherical shape. The pellet can be built up to provide the required mechanical strength by repeating the coating process as required. A biodegradable barrier coating capable of being degraded by the action of ruminal fluids is then applied around the coated core by any suitable process. The coating forms an impermeable barrier which only starts to be broken down when contacted by ruminal fluids.

The nature of the biodegradable barrier together with its thickness is

critical in determining the time required to break down the material. The pellets may be coated with different thicknesses of biodegradable material to give different release profiles, or alternatively coated with different materials having distinct release profiles. The materials used are, preferably polymers, the preferred polymers being polyesters, such as polylactic acid, polyglycolic and polybutyric acid polymers and co-polymers. In one particularly preferred form the biodegradable barrier used is formed from 100% poly-L-lactic acid or a 85/15% mixture of poly-L-lactic/poly-L-glycolic acid polymers dissolved in acetone (10% w/v). For a given thickness the 100% poly-L-lactic acid barrier would be the first to degrade, followed by the 85/15% mixture. Depending on processing techniques the pellets may have a barrier thickness of between about 10 micrometers to 150 micrometers. The different composition and thickness permit significantly different degradation characteristics to be incorporated into the respective pellets of the group.

The carrier 2 is weighted by the ballast 6 which ensures that the device is retained in the rumino-reticular sac. The ballast provides a density of from 1.5 to 4.0 g/c^3, with a density of 2.5 to 3.5 g/c^3 being preferred for devices intended for use with cattle and sheep. In the form shown, the ballast is provided in a housing 16 attached to the base of the carrier 2. The housing 16 has a part-spherical end and houses the ballast 6 which may be in the form of iron, iron/magnesium alloy, steel, copper oxide and mixtures thereof. It is preferred for the ballast to be in the form of finely divided particles to permit speedy break down of the ballast and also to facilitate elimination from the animal at the end of the working life of the device. The finely divided particles of ballast may be bound into a cohesive body by a water soluble binder such as a starch or cellulose-based material which breaks down in the presence of ruminal fluids. The housing 16 containing the ballast 6 is permanently attached to the carrier 2, for example by means of a snap-type or screw-type locking connection, or by ultrasonic or heat-induced welding, or by use of a suitable adhesive.

The construction of the device is such as to prevent ruminal fluids from

contacting the ballast 6 until such a time has elapsed that release of substance from the final pellet of the sequence has substantially finished. This can be achieved in various ways. In the particular form shown, this is achieved by forming the carrier 2 with a base 20 which closes the upper open end of the housing 16. The base 20 has an aperture 22 which is closed by the bottom-most pellet 4 within the central passage 10 of the carrier, this pellet being the final pellet in the sequence. The presence of the bottom pellet thus precludes access of ruminal fluids to the ballast 6 via the aperture 22. The ruminal fluids are thus prevented from contacting the ballast until the core of the final pellet has dissolved to a sufficient extent to permit passage of ruminal fluids through the aperture 22 into contact with the ballast 6. In an alternative configuration, the upper open end of the housing 16 may be closed by a biodegradable membrane which prevents access of ruminal fluids to the ballast 6, but which degrades after a period of time longer than the degradation time required for the final pellet. Alternatively, the ballast 6 may be fully enclosed within the housing 16, with the housing 16 being wholly or partly constructed of a biodegradable material having a degradation time within the rumen longer than that of the final pellet of the sequence. Contact of the ruminal fluids with the ballast 6 will break down the binder, thereby permitting release of the finely divided particles of the ballast which are expelled by excretion. The carrier 2 and ballast housing 16 (if the housing is not itself formed from material which is biodegraded by ruminal fluids) can then, due to the reduced density, be expelled by regurgitation or excretion.

The carrier 2 and ballast housing 16 may be formed from a polymeric material such as high or low density PVC. It is preferred however that the polymeric material is a photo-degradable polymer such that on being discharged from the animal it will break down under the exposure to ultra- violet radiation, preferably within a few days. The material may alternatively be a polymeric material which is bacterially degradable, for example a cellulosic polymeric material or a chitin-containing polymeric material. The particular material chosen will be chemically-inert and non-toxic.

For some applications, particularly for use in sheep, ballasting alone may not be sufficient to retain the device within the rumen, and in such a case the carrier can include additional means such as expandable wings or filaments which ensure retention for the required time.

The overall device as described is relatively compact, typically about 5 cm in length and 2.5 cm in diameter. The lower end of the ballast housing 20 is of part-spherical form and the device may thereby be orally introduced using a standard balling gun.

The pellets themselves are relatively inexpensive to produce and the pulsed release characteristics are determined simply by means of the characteristics of the outer impermeable barrier on each individual pellet. The carrier and housing of the device can also be inexpensively produced by mass-production techniques, for example by injection moulding.

The device according to Figures 1 to 5 was tested in a convenient laboratory model to demonstrate the sequential release of a substance from pellets 4. The medium used for testing the model was designed to accelerate the degradation of the outer barrier of each pellet 4. The intra-ruminal device contained two pellets 4 coated with different biodegradable polymers designed to give a differential release rate of marker substances contained therein (namely at about 2 hours and 5 hours of incubation). For ease of analysis, one pellet 4 contained the dye Orange G (designed for release at about 2 hours and detectable at a wave length of 492 nm) and the other contained the dye Pontamine Sky Blue (designed for release at about 5 hours and detectable at 620 nm). The intra-ruminal device was placed in a 1 litre container filled with the accelerated ageing medium consisting of 0.1 M NaOH, 10% Ethanol (v/v), and 0.9% NaCl. The device was placed on a perforated stainless steel stage above a magnetic stirrer to provide constant movement of fluid media around the device. Under these conditions each barrier coating degraded within hours and sequentially released the dyes into the medium illustrated in Figure 6. As

expected, the dye Orange G was released into the medium at about 2 hours after incubation and the dye Pontamine Sky Blue was released into the medium at about 5 hours of incubation. This pulsatile sequential release is consistent with differential degradation of the biodegradable polymers coating each pellet 4. This experiment shows that material contained within pellets 4 can be effectively released in pulsatile fashion over a differential time period. This in-vitro model is directly applicable to the in-vivo situation within the rumen of an animal where pulsatile differential release of active components (in place of dye compounds) would take place.

As explained earlier, pulsatile release in a series of spaced pulses can also be achieved by means of a single pellet mounted within an open structure of the type shown in the drawings. A pellet suitable for this purpose can comprise a series of concentric alternating layers consisting of impermeable barrier layers and layers of the substance. Such a pellet can be constructed using the techniques described previously by forming a core, applying an inner barrier layer around the core, and then applying a further layer of substance around the inner barrier layer, followed by a further barrier layer, and repeating the process to provide the required number of layers. Although this pellet requires more manufacturing steps than a pellet having a single layer of substance, nevertheless it can still be manufactured relatively simply and inexpensively.

If a pulsed release in a single dose is required the open structure can contain a single pellet consisting of a core of the substance, with an outer impermeable coating formed as previously described to provide the release at a predetermined time (for example several weeks) after administration.

If required the pellet (in the case of a single pellet) or one of the pellets may include an external layer of substance outside of the impermeable barrier to provide a dose of substance on administration of the device, followed by a further dose at a later time determined by the characteristics of the impermeable barrier.

The device particularly described including the pellets which can be manufactured using simple techniques, enables pulsatile administration of substance to ruminant animals either in a series of doses or in a single dose at a predetermined time after administration to provide a more effective and controllable treatment for the animal.

The embodiment has been described by way of example only and modifications are possible within the scope of the invention.

CLAIMS

1. A device for release of substance into the rumen of an animal, said device comprising a body carrying at least one pellet including substance to which access of ruminal fluids is initially prevented by an impermeable barrier which degrades when exposed to ruminal fluids, the body having an open structure to permit contact of ruminal fluids with the or each of the pellets, and said device being such that the device will remain within the rumen for a period of time sufficient to enable release of substance from the or each of the pellets.

2. A device according to claim 2, wherein the impermeable barrier of the or each pellet comprises a coating layer on the pellet, the degradation rate of the coating being dependent on the thickness and/or composition of the coating.

3. A device according to claim 2, wherein the impermeable barrier forms the outer surface of the pellet or of at least some of the pellets.

4. A device according to claim 1, wherein the pellet comprises several concentric layers consisting, alternately, of a layer of substance coated with an impermeable barrier layer which degrades when exposed to ruminal fluids.

5. A device according to any one of claims 1 to 3, comprising a plurality of said pellets carried by the body such that substantially simultaneous contact of ruminal fluids can occur with each of the pellets, the impermeable barrier of each respective pellet being such that the time required to degrade the barrier differs from pellet to pellet.

6. A device according to claim 5, wherein the impermeable barriers of the respective pellets are such that release of substance from the respective pellets occurs at spaced intervals whereby release of substance from one pellet does not occur until a predetermined period of time after release of substance from another pellet has been completed.

7. A device according to any one of claims 1 to 6, in which the body is of a cage-like structure and includes means for locating the or each said pellet in a discrete position within the structure.

8. A device according to any one of claims 1 to 7, wherein the device is such that retention within the rumen for the required period of time is provided at least partially by the density of the device.

9. A device according to claim 8, wherein the device includes ballast which is released after a predetermined period of time to permit expulsion of remaining parts of the device from the rumen.

10. A device according to claim 9, wherein the device includes a housing within which the ballast is enclosed, the ballast comprises matter which is broken down on contact by ruminal fluids, and the housing is such that contact of the ballast within the housing by ruminal fluids is prevented until the device has been within the rumen for a predetermined period of time.

11. A device according to claim 10, wherein the housing is at least partially defined by a material which degrades when exposed to ruminal fluids whereby access of ruminal fluids to the ballast occurs as a result of degradation of said material.

12. A device according to claim 10, wherein access of ruminal fluids to the ballast is via a passage which communicates with the open structure of the body, the passage initially being blocked by one said pellet and being opened by progressive dissolution of that pellet.

13. A device according to claim 12 when dependent on claim 5, wherein the said one pellet is the pellet having an impermeable barrier which has the longest degradation time of the impermeable barriers of the group of pellets.

14. A device according to any one of claims 10 to 13 when dependent on claim 7, wherein the housing and the cage-like structure are separate components secured together.

15. A device according to any one of claims 1 to 8, wherein retention of the device within the rumen for the required period of time is provided at least partially by the geometry of the device.

16. A device according to any one of claims 1 to 15, wherein the or each said pellet comprises a core containing the substance.

17. A device according to claim 16, wherein the surface of the core is coated to provide mechanical strength.

18. A device according to claim 17, wherein the impermeable barrier consists of a layer applied to the coated surface of the core.

19. A device according to any one of claims 16 to 18, wherein the or each said pellet is substantially spherical.

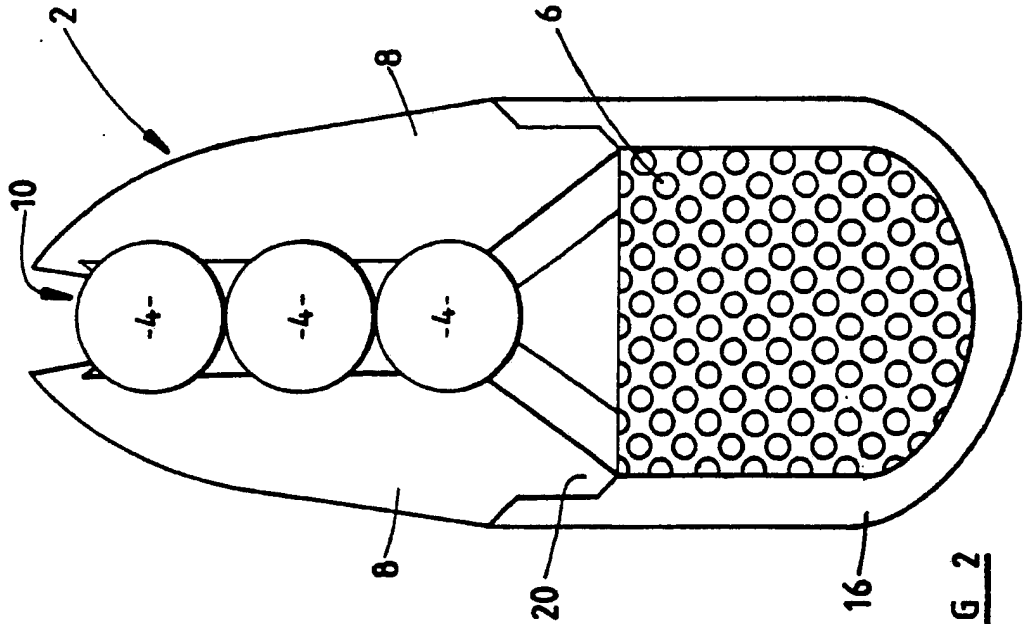


FIG 2

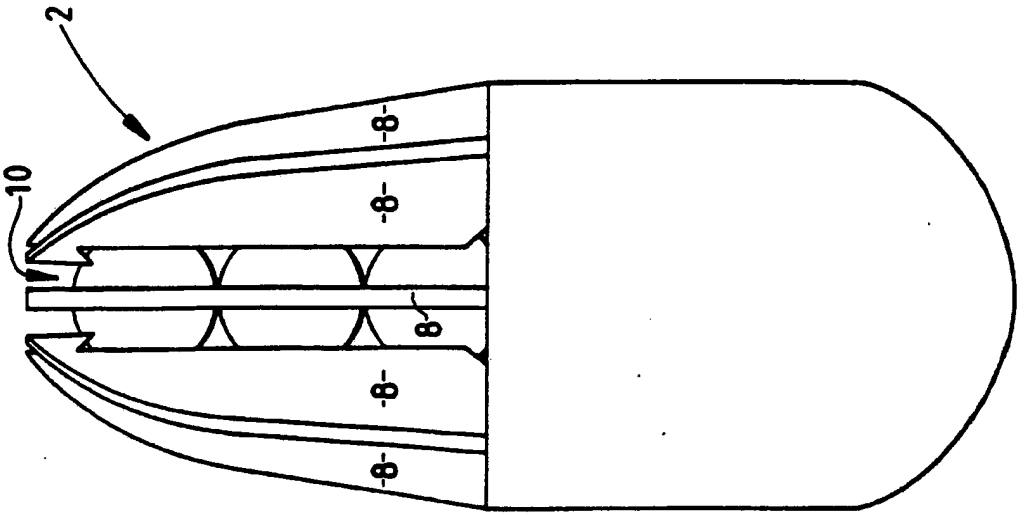


FIG 1

FIG 3

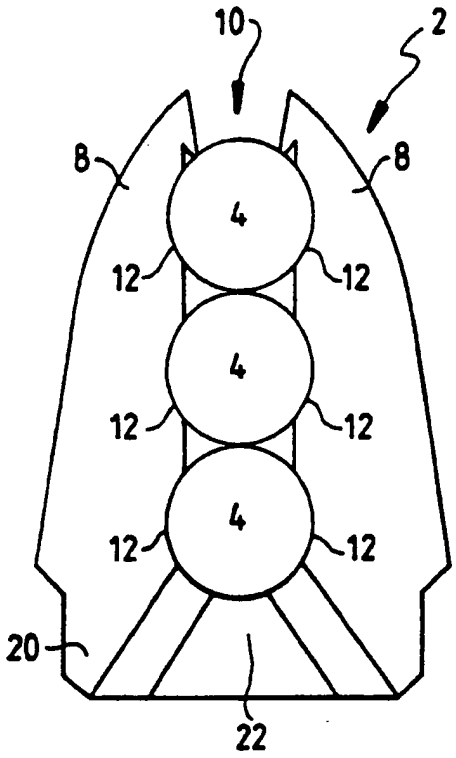


FIG 4

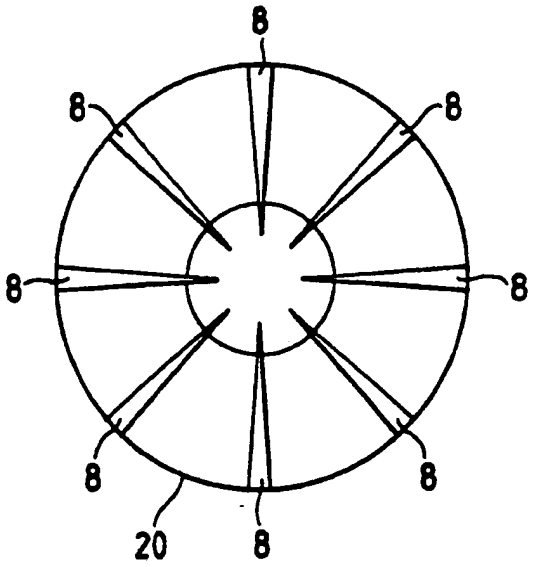
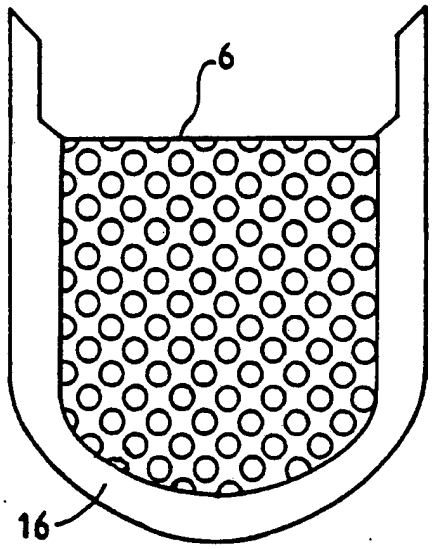
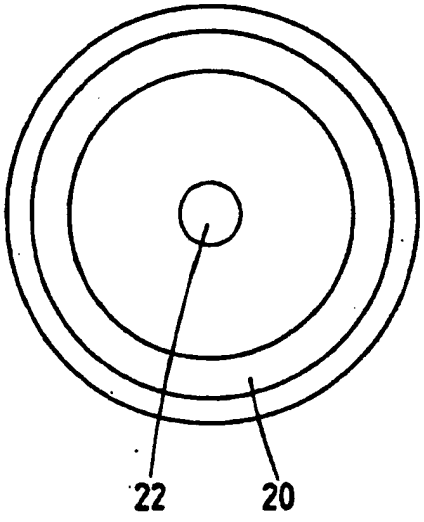


FIG 5





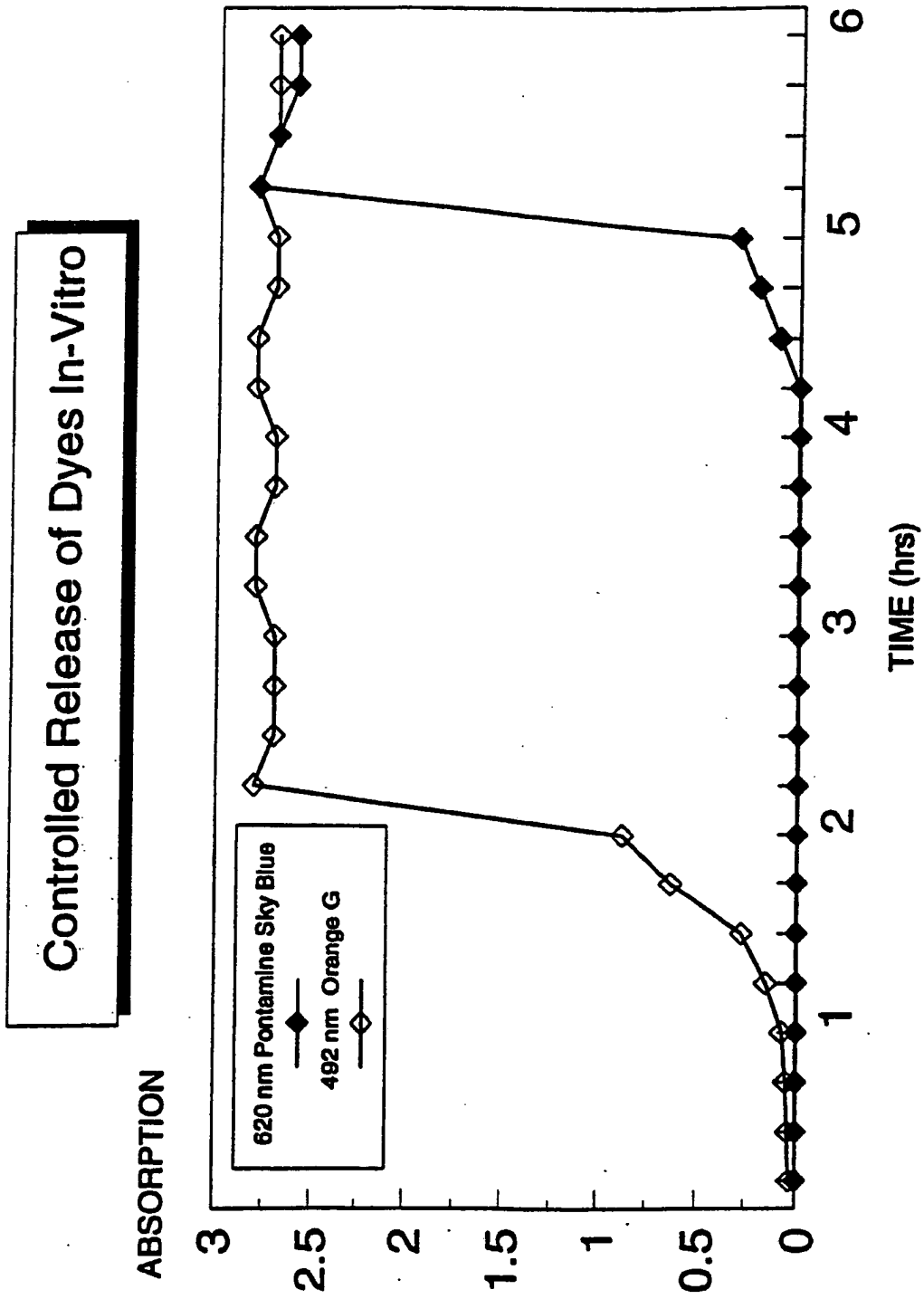

Controlled Release of Dyes In-Vitro
ABSORPTION
TIME (hrs)
620 nm Pontamine Sky Blue
492 nm Orange G
0
0.5
1
1.5
2
2.5
3
1
2
3
4
5
6

FIG. 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU93/00112

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl.[5] A61D 7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61D 7/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC as above

Electronic data base consulted during the international search (name of data base, and where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,X	AU,A,10457/92 (HOECHST AKTIENGESELLSCHAFT) 30 July 1992 (30.07.92) page 11, line 26-31 and figure 3	1-3,5,6,15,16,19
X	EP,A,242053 (STC PLC) 21 October 1987 (21.10.87) page 2 line 44 - page 3 line 11	1, 4-7
Y		2,3,8-11,14-16,19
Y	EP,A,373890 (COOPERS ANIMAL HEALTH LIMITED) 20 June 1990 (20.06.90) column 4 lines 23-40	8,9,10

[X] Further documents are listed in the continuation of Box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
3 June 1993 (03.06.93)	18 JUNE 1993 (18.06.93)
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No. 06 2853929	Authorized officer A. HENDRICKSON Telephone No. (06) 2832415

Form PCT/ISA/210 (continuation of first sheet (2)) (July 1992) copjll

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate of the relevant passages	Relevant to Claim No.
X,Y	US,A,4381780 (HOLLOWAY) 3 May 1983 (03.05.83) column 3 lines 29-67, column 4 lines 14-16, column 5, lines 6-8	1-6, 8
Y		7,9-11,15,16,19
X,Y	GB,A,2186291 (CASTEX PRODUCTS LIMITED) 12 August 1987 (12.08.87) page 4 lines 35-43 and 54-59	1, 8-11, 14
Y		2-7, 15, 16, 19
Y	AU,B,25802/77 (514312) (MALZ NOMINEES PTY LTD) 7 December 1978 (07.12.78) page 2 lines 14-19	15, 16, 19

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